PEDF Is a Novel Oligodendrogenic Morphogen Acting on the Adult SVZ and Corpus Callosum.

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Public Summary:
Pigment epithelium-derived factor (PEDF) is a serine protease inhibitor (serpin) protein with well established neuroprotective and anti-angiogenic properties. Recent studies have also shown that PEDF enhances renewal of adult subventricular zone (SVZ) neural precursors. In neurosphere cultures prepared from the SVZ of adult mice, we found that addition of recombinant PEDF to the medium enhanced expressions of oligodendroglial lineage markers (NG2 and PDGFrα) and transcription factors (Olig1, Olig2, and Sox10). Similarly, continuous PEDF administration into the lateral ventricles of adult glial fibrillary acidic protein:green fluorescent protein (GFAP:GFP) transgenic mice increased the proportions of GFAP:GFP+ and GFAP:GFP- SVZ neural precursors coexpressing oligodendroglial lineage markers and transcription factors. Notably, PEDF infusion also resulted in an induction of doublecortin- and Sox10 double-positive cells in the adult SVZ. Immunoreactive PEDF receptor was detectable in multiple cell types in both adult SVZ and corpus callosum. Furthermore, PEDF intracerebral infusion enhanced survival and maturation of newly born oligodendroglial progenitor cells in the normal corpus callosum, and accelerated oligodendroglial regeneration in lysolecithin-induced corpus callosum demyelinative lesions. Western blot analysis showed a robust upregulation of endogenous PEDF in the corpus callosum upon lysolecithin-induced demyelination. Our results document previously unrecognized oligodendrotrophic effects of recombinant PEDF on the adult SVZ and corpus callosum, demonstrate induction of endogenous CNS PEDF production following demyelination, and make PEDF a strong candidate for pharmacological intervention in demyelinative diseases.

Scientific Abstract:
Pigment epithelium-derived factor (PEDF) is a serine protease inhibitor (serpin) protein with well established neuroprotective and anti-angiogenic properties. Recent studies have also shown that PEDF enhances renewal of adult subventricular zone (SVZ) neural precursors. In neurosphere cultures prepared from the SVZ of adult mice, we found that addition of recombinant PEDF to the medium enhanced expressions of oligodendroglial lineage markers (NG2 and PDGFralpha) and transcription factors (Olig1, Olig2, and Sox10). Similarly, continuous PEDF administration into the lateral ventricles of adult glial fibrillary acidic protein:green fluorescent protein (GFAP:GFP) transgenic mice increased the proportions of GFAP:GFP+ and GFAP:GFP- SVZ neural precursors coexpressing oligodendroglial lineage markers and transcription factors. Notably, PEDF infusion also resulted in an induction of doublecortin- and Sox10 double-positive cells in the adult SVZ. Immunoreactive PEDF receptor was detectable in multiple cell types in both adult SVZ and corpus callosum. Furthermore, PEDF intracerebral infusion enhanced survival and maturation of newly born oligodendroglial progenitor cells in the normal corpus callosum, and accelerated oligodendroglial regeneration in lysolecithin-induced corpus callosum demyelinative lesions. Western blot analysis showed a robust upregulation of endogenous PEDF in the corpus callosum upon lysolecithin-induced demyelination. Our results document previously unrecognized oligodendrotrophic effects of recombinant PEDF on the adult SVZ and corpus callosum, demonstrate induction of endogenous CNS PEDF production following demyelination, and make PEDF a strong candidate for pharmacological intervention in demyelinative diseases.